~~CASWELL FILE~~

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005126

MAY 17 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: I.D. Number 476-1819; Captan: Special mouse oncogenicity study.
Tox. Chem. No.: 159

TO: H. Jacoby (PM 21)
Registration Division (TS-767C)

FROM: Marion P. Copley, D.V.M., D.A.B.T. MPC 5/16/86
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Jane Harris, Ph.D., Section Head JEH 5/16/86
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C) [illegible] 5/17/86

Stauffer has submitted a special mouse oncogenicity study using 6000 ppm of captan in the diet (see the attached data evaluation report).

This is a well designed study to investigate the mechanism of intestinal neoplasia due to captan. It would have been useful however, if the company had investigated captan's hyperplastic and neoplastic potential at doses lower than 6000 ppm as well.

It is apparent from this study that 6000 ppm of captan is associated with a decreased time to lesion and higher incidence of both duodenal hyperplasia and neoplasia. The data supports the hypothesis that over an 18 month study period, mucosal hyperplasia may regress if the insult is removed after 6 months of exposure. However, the hyperplasia does have the potential to progress to benign or malignant lesions when treatment is continued for 9 to 12 months.

BACKGROUND:

Captan is currently under special review (Position document 2/3 is completed) and a Registration Standard was completed in March 1986. The following data gaps still exist for captan:

- Acute dermal toxicity
- Primary dermal irritation
- 21-day dermal toxicity
- Chronic (oral) - non-rodent
- Subchronic (inhalation)
- Metabolism

Reviewed by: Mari P. Copley, D.V.M., D.A.I 7/15/86
Section VI, Tox. Branch (TS-769C)
Secondary reviewer: Jane Harris, Ph.D.
Section VI, Tox. Branch (TS-769C)

005126

DATA EVALUATION REPORT

STUDY TYPE: chronic feeding (special) - mouse

TOX. CHEM. NO.: 159

ACCESSION NUMBER: 259578

TEST MATERIAL: captan technical

SYNONYMS: N-trichloromethylthio-4-cyclohexene-1,2-dicarb (a.i.)

STUDY NUMBER(S): T-11007

SPONSOR: Stauffer

TESTING FACILITY: Stauffer Env. Health Ctr., Farmington, Conn.

TITLE OF REPORT: Identification of a preneoplastic alteration following dietary administration of captan technical to CD-1 mice

AUTHOR(S): K.L.Pavkov, R.W.Thomassen, G.L.Sprague, G.W.Zwicker, D.R.Saunders

REPORT ISSUED: 9/23/85

CONCLUSIONS:

Statistical increase in intestinal hyperplasia by 3 months.
Statistical increase in intestinal adenomas by 9 months, adenocarcinomas by 18 months.

Classification: core-supplementary due to the special nature of the study; males only; dose levels: 0 and 6000 ppm (900 mg/kg/day).

A. MATERIALS:

1. Test compound: Captan technical; Description: white to buff colored powder, composite lot # EHC-0355-27; Purity: 89.1 % a.i.

2. Test animals: Sex: male; Species: mouse; Strain: CD-1; Age: 40 days at start of study; Weight: Not given; Source: Charles River Breeding Labs., Kingston, N.Y.

B. STUDY DESIGN:

1. Animal assignment - Healthy animals were assigned to the following study groups such that all groups had similar mean body weights and standard deviations. Male mice were treated with either 0 or 6000 ppm captan technical in the diet for the following time periods: 3, 6, 9, 12, or 18+* months. A second group (6000A) was treated for 6 months and allowed to recover for either 6 [6/6]** or 12 [6/12] months. The third group (6000B) was treated for 12 months and allowed to recover for 6 to 8 months* [12/6].

* The company combined animals sacrificed at 18 and 20 months for statistical purposes and referred to them as 18+.
** [a/b] duration of captan treatment/duration of recovery period

005126

Other parameters examined at necropsy (10 mice/sacrifice period) included iron accumulation, radioautography, special histochemical tests and nonprotein bound reduced sulfhydryls. The number of mice sacrificed for histologic examination are given in Table 3 from the report:

Table 3. The Number of Mice Sacrificed at Each Interval

Treatment group/ dose level (ppm)	Treatment period (mo)	Recovery period (mo)	Number sacrificed at each interval (mo)				
			3	6	9	12	18+
0	lifetime	0	20	20	20	20	26
6000	lifetime	0	20	20	20	18*	22
6000A	0 to 6	7 to 12				10	
		7 to 18					16
6000B	0 to 12	13 to 18					10
		13 to 20					14

* Two iron injected mice died after the injection and prior to sacrifice. No substitution was made.

2. Diet preparation - Diet/compound was prepared biweekly for 6 weeks, then monthly; storage temperature was unspecified. Samples (stratified sampling technique) of treated food were analyzed for concentration and homogeneity, weekly for 4 weeks then monthly. There were 22 sampling times, consisting of 9 sample points each.

   Results - The average concentration over all time periods was 5982.7 ppm a.i. with a standard deviation (SD) of 385.9 ppm. The minimum and maximum mean concentrations for the sampling dates ranged from 5400 to 7100 ppm. The percent SD ranged from 1.7 to 4.5 (the SD in one period was 10 % of the mean).

3. Animals received food (Purina Certified Rodent Chow Meal 5002) and water ad libitum.

4. Statistics - The following procedures were utilized in analysing the numerical data: A one way analysis of variance and Dunnett's Test were used for body weight, food consumption and compound consumption. The chi^2 test was used to compare non-neoplastic and neoplastic lesion frequencies between the control and treatment groups. These lesions were also compared for trend (test unspecified) with respect to duration of treatment and recovery period.

005126

5. There was a signed quality assurance statement that the "reported results accurately reflect the data for this study."

C. METHODS AND RESULTS:

1. Observations - Animals were examined twice daily for signs of toxicity and mortality. They were given a more detailed physical examination (including palpation) every other week.

   Results - Toxicity - There were no treatment related signs of toxicity noted during the study period.

   Mortality - Mortality rate was not affected by treatment with captan at 6000 ppm in the diet.

2. Body weight - They were weighed every two weeks for 96 weeks, then monthly for the remainder of the study.

   Results - There were reductions in weight gain (5-14%) for mice in all three 6000 ppm treatment groups as compared to controls. Table is from the report.

Table 5. Body Weight Change

Dose group	Percent of initial weight		
	Week 31	Week 53	Week 75
Control	147	150	147
6000 ppm	130	133	140
6000 ppm (recovery group A)	130	137	133
6000 ppm (recovery group B)	126	132	132

3. Food consumption and compound intake - Consumption was measured every two weeks for 56 weeks, then monthly for the remainder of the study. The mean daily diet consumption was calculated. Compound intake was calculated from the consumption and body weight gain data.

   Results - Food consumption in all treatment groups was significantly lower than controls (between 5 and 10 %) until week 40. After which time only the 6000 group (no recovery) remained lower.

   Compound intake - The average daily intake for all three treatment groups (during the treatment period) ranged from 660 to 719 mg/kg/day.

4. Ophthalmalogical examinations were not performed.

5. Blood was not collected for hematology and clinical chemistries.

6. Urinalysis were not performed.

005126

7. Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Organ weights were not obtained.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
X	Tongue		Aorta*		Brain*
	Salivary glands*		Heart*		Periph. nerve*
X	Esophagus*		Bone marrow*		Spinal cord (3 levels)*
X	Stomach*		Lymph nodes*		Pituitary*
X	Duodenum*		Spleen*		Eyes (optic n.)*
X	Jejunum*		Thymus*		Glandular
X	Ileum*		Urogenital		Adrenals*
X	Cecum*		Kidneys*		Lacrimal gland
X	Colon*		Urinary bladder*		Mammary gland*
X	Rectum*		Testes*		Parathyroids*
	Liver*		Epididymides		Thyroids*
	Gall bladder*		Prostate		Other
	Pancreas*		Seminal vesicle		Bone*
	Respiratory		Ovaries		Skeletal muscle*
	Trachea*		Uterus*		Skin
	Lung*				All gross lesions and masses

Histology was limited to the gastrointestinal (GI) tract. The entire GI tract was rapidly removed, fixed and external abnormalities (including dilatation) were noted. The entire length of the GI tract was examined histologically (in "Swiss rolled" segments) using a hematoxylin and eosin stain. Non-neoplastic lesions were graded from 1 to 5 (5 being the most severe). Severity and width were both considered when scoring focal epithelial hyperplasia of the small intestine. Attached (appendix 1) are the company's criteria for the proliferative epithelial lesions of the small intestine.

Special tests performed on selected mice included:

1) Spectrophotometric analysis for nonprotein-bound reduced sulfhydryls;
2) Iron uptake after a presacrifice injection of iron dextran. After sacrifice, the small intestine was sectioned and stained by the Perl's reaction to produce Prussian blue pigment indicative of iron deposition;
3) Small intestine sections were also stained for mucosubstances;
4) Enzyme histochemistry - alkaline phosphatase reaction (AP), glucose-6-phosphate dehydrogenase reaction (G6PDH), and gamma-glutamyl transpeptidase reaction (GGT);
5) Radioautography with a cresyl violet counterstain following a presacrifice injection of H^3-thymidine ip.

* Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

005126

Results -

a. Gross pathology - Lesions of the small intestine that occurred primarily or exclusively in captan treated mice included dilatation, mucosal thickening, invagination and dimpling of the wall and a prominence of serosal vasculature. Dilatation occurred in 80 % of the treated mice by 6 months. Only 1 control mouse (at 18 months) had dilatation.

b. Special tests - According to the report, the special tests did not assist in the diagnosis of non-neoplastic or neoplastic lesions.

c. Microscopic pathology - Appendix 2 (attached) includes tables 7, 8, 11, 14, 15 and 16 from the report.

1) Non-neoplastic - Hyperplasia in the stomach occurred only in the nonglandular portion (at 3 months). Intestinal hyperplasia was observed at 3 months (75 %) in treated animals but not until 12 months (25 %) in the controls (table 7, 8). After 6 months of treatment followed by 6 or 12 months of recovery, the incidence of hyperplasia was not increased over controls (table 7). When treatment of 12 months was followed by 6 months recovery, hyperplasia (29 %) was increased (not statistically), over controls (19 %)(table 7). Focal, rather than diffuse hyperplasia, was the most common intestinal lesion. In the controls, 28 % of the focal hyperplasias occurred in the proximal 7 cm of the small intestine and 83 % within 14 cm (table 14). In treated mice, with no recovery, most (95 %) focal hyperplastic lesions occurred within 7 cm of the pylorus (99 % within 14 cm)(table 15). The distribution more closely resembled that of controls when mice treated for 6 or 12 months were allowed to recover for an additional 6 or 12 months (table 16).

2) Neoplastic - There was a significant ($p < .01$) increased incidence (25 %) of tumors (adenomas) in treated mice sacrificed at 9 months as compared to a control incidence of 0 % (a nonstatistically significant increase of 10 % occurred at 6 months)(table 8). There were no tumors in the controls until 18 months (1 adenocarcinoma, 4 % incidence) (table 8). Animals in the 6000A group [6/6] had a statistically significant increased incidence in tumors (20 %) in comparison with controls (0 %). Although those allowed a 12 month recovery [6/12] still had an increased incidence in tumors (19 %) as compared to controls (4 %), it was not statistically significant. In group 6000B [12/6], there was a statistically significant increase in tumors (42 %) in comparison to controls (4 %)

(table 7). An increased incidence of malignant duodenal tumors occurred only at the 18+ month sacrifices in mice treated for 12 or 18 months (table 7). Tumors in the treated animals (including recovery groups) were usually located within the first 7 cm of the small intestine (table 15, 16) while those in the control groups were primarily 7 to 14 cm from the pylorus (table 14).

D. DISCUSSION:

This is a well designed and performed study to investigate the mechanism of intestinal neoplasia in CD-1 mice due to captan. It would have been useful however, if the company had investigated captan's hyperplastic and neoplastic potential at doses lower than 6000 ppm as well. The company concluded that histopathologic examination of the entire intestinal tract (in rolled segments) was more consistent in diagnosing intestinal hyperplasia and neoplasia than the special tests often used to aid in the diagnosis of other tumor types.

Although weight gain and food consumption were both depressed, with the exception of hyperplasia and neoplasia, there was no other evidence of marked toxicity with 6000 ppm of captan in the diet of male mice.

There is a statistical increased incidence in treated mice as compared to control in intestinal hyperplasia and adenomas located within the first several centimeters past the pylorus. This occurs within the first 3 months for hyperplasia and 9 months for neoplasia. An increased incidence of malignant neoplasia does not occur however, until 12 or 18 months of treatment. A 6 to 12 month recovery period following 6 to 12 months of treatment resulted in a decreased incidence of hyperplasia in comparison to treatment animals sacrificed at 6 to 12 months.

The data supports the hypothesis that over an 18 month study period, mucosal hyperplasia may regress if the insult is removed after 6 months of exposure. However, the hyperplasia does have the potential to progress to benign or malignant lesions when treatment is continued for 9 to 12 months.

T-11007: IDENTIFICATION OF NEOPLASTIC ALTERATION FOLLOWING DIETARY ADMINISTRATION OF CAPTAN TECHNICAL TO CD-1 MICE

APPENDIX 1

005126

The following criteria were followed in the diagnoses of proliferative epithelial lesions of the small intestine:

1) Diffuse hyperplasia of crypt columnar epithelial cells

This diagnosis denotes an increase in the number of crypt base or midcrypt columnar epithelial cells in many adjacent intestinal glands that consequently results in a lengthening or increased depth of the glands. The villus crypt ratio is about 3:1 (normal ratio of 4:1 or 5:1). The area of hyperplasia usually exceeds 2 or more widths of the 6.3x objective field. The hyperplastic cells show no loss of differentiation (atypia) and other tissues of the intestine are normal.

2) Focal hyperplasia of crypt columnar epithelial cells

This diagnosis denotes an increase in the number of crypt base or midcrypt columnar epithelial cells in a few or several adjacent intestinal glands that consequently results in considerable lengthening of the crypts. The villus:crypt ratio may range from 2:1 to 0:n. A ratio of 0:n describes an essentially avillus lesion in which the intestinal glands open at or near the surface of the mucosa. The lesion may not be elevated above the surrounding mucosa (flat focus) or the hyperplasia may result in a focally thickened or elevated mucosa (raised focus). Polypoid lesions may be present with broad (sessile) or narrow (pedunculated) bases. The lengthened crypts generally maintain a straight alignment, with most cross section configurations being explained by the plane of cut. Crypt dilatation is nonexistent or minimal. Proliferating cells may be morphologically normal or exhibit atypia (variation in size and shape, loss of orientation, increased cytoplasmic basophilia or mitotic figures). Cells at the extrusion zone of villus tips are nearly always abnormal with poor staining and frayed appearance. The lamina propria may be normal or may be edematous and/or contain excessive numbers of lymphocytes and/or plasma cells. The submucosa may be normal or may be edematous, fibrotic, and/or infiltrated by lymphocytes and/or plasma cells. The submucosal arteries and veins are often ectatic (dilated). The tunica muscularis is generally thickened throughout the entire width of the lesion. In some instances there is marked thickening due to hyperplasia of the inner circular muscle layer. Other basilar crypt cells (Paneth and argentaffin cells) are not increased in number; however, clusters of normal appearing Paneth cells may be seen in superficial regions of a lesion.

3) Microfocal hyperplasia of epithelial cells

This denotes a minute focus of proliferating intestinal gland or villus columnar epithelial cells that is not associated with lengthened or hyperplastic crypts. Most of these foci appear to be areas near the periphery of larger areas of focal hyperplasia; however, examination of replicate sections did not connect them with larger foci.

4) Intestinal adenoma

This diagnosis denotes a benign neoplasm of columnar epithelial cells. Adenomas are distinguished by: (1) extensive elongation of crypts that produces an essentially avillus surface over much of the lesion, and (2) coiling of lengthened glands that produces a local or generalized adenomatous appearance. Crypt lumens may be slightly dilated. Varying degrees of epithelial atypia are seen but are never present as anaplasia. Foci of hyperplastic Paneth cells may be present. Hyperplasia of the tunica muscularis is usually prominent. Proliferating epithelium and muscle may meet but there is no unequivocal penetration of the muscle by dysplastic glandular cells. The lamina propria and submucosa usually contain lymphocytes and plasma cells. Submucosal fibrosis is usually seen but never has the appearance of a desmoplastic reaction to neoplastic epithelium. Ectatic submucosal arteries and veins are common. The surface of most adenomas project above the level of adjacent mucosa. Most adenomas lip-over at the margins. Some are polypoid and others have filiform or papillary surfaces.

5) Intestinal adenocarcinoma

This diagnosis denotes a malignant neoplasm of columnar epithelial cells in which there is unequivocal invasion of the tunica muscularis and/or serosa by dysplastic epithelial cells and/or metastasis of neoplastic epithelium to regional lymph nodes or other organs. Cellular atypia and glandular dilatation may be prominent. Large cysts are generally formed when the serosa is invaded.

Table 7. Incidence of Hyperplastic and Neoplastic Epithelial Lesions of the Small Intestine

	Treatment												
	Lifetime without captan					Lifetime with captan					Part-time with captan		
Dose level (ppm):	0					6000					6000		
Treatment period (mo):	0-3	0-6	0-9	0-12	0-18+	0-3	0-6	0-9	0-12	0-18+	0-6[a]	0-6[b]	0-12[c]
Study age at death (mo):	3	6	9	12	18+	3	6	9	12	18+	12	18	18+
No. of animals	20	20	20	20	26	20	20	20	18	22	10	16	24
No. of animals with lesions	0	0	0	5	6	15	20	18	18	22	3	4	16
No. with hyperplasia	0	0	0	5	5	15	20	17	18	22	1	2	7
Diffuse	0	0	0	0	0	7	8	3	3	3	0	0	0
Microfocal	0	0	0	2	1	0	0	0	0	1	1	2	3
Focal	0	0	0	3	5	14	19	17	17	22	1	2	6
No. with neoplasia	0	0	0	0	1	0	2	5	3	8	2	3	10
Benign	0	0	0	0	0	0	2	5	3	4	2	1	5
Malignant	0	0	0	0	1	0	0	0	0	6	0	2	7

[a] Recovery period 7 through 12 months.
[b] Recovery period 7 through 18 months.
[c] Recovery period 13 through 18+ months.

T-11007

005126

Table 8. Summary of Incidence of Hyperplastic and Neoplastic Epithelial Lesions of the Small Intestine in Mice Given Captan (6000 ppm) in Diet

	Treatment period (mo)					
	3	6	9	12	18+	
Number of animals						Statistical interpretation of trend
control:	20	20	20	20	26	
captan-treated:	20	20	20	18	22	
Any lesion						
control:	0	0	0	25[a]	23	A ($p<0.01$)
captan-treated:	75*	100*	90*	100*	100*	B ($p<0.01$)
Any hyperplasia						
control:	0	0	0	25	19	A ($p<0.01$)
captan-treated:	75*	100*	85*	100*	100*	B ($p<0.01$)
Diffuse hyperplasia						
control:	0	0	0	0	0	NS
captan-treated:	35	40	15	17	14	C ($p<0.05$)
Microfocal hyperplasia						
control:	0	0	0	10	4	NS
captan-treated:	0	0	0	0	4	NS
Focal hyperplasia						
control:	0	0	0	15	19	A ($p<0.01$)
captan-treated:	70*	95*	85*	94*	100*	B ($p<0.01$)
Any neoplasia						
control:	0	0	0	0	4	NS
captan-treated:	0	10	25**	17	36*	B ($p<0.01$)

[a] - Data are expressed as percentage of animals with the lesion.
NS - Not significant.
A - Significant trend toward increasing incidence with increasing age.
B - Significant trend toward increasing incidence with increasing age and continuous captan treatment.
C - Significant trend toward decreasing incidence with increasing age and continuous captan treatment.
* Significantly greater incidence than in controls of the same age ($p<0.01$).
** Significantly greater incidence than in controls of the same age ($p<0.025$).

Table 11. Average Number of Hyperplastic and Neoplastic Epithelial Lesions of the Small Intestine in Mice Given Captan in Diet

	Treatment												
	Lifetime without captan					Lifetime with captan					Part-time with captan		
Dose level (ppm):	0					6000					6000		
Treatment period (mo):	0-3	0-6	0-9	0-12	0-18+	0-3	0-6	0-9	0-12	0-18+	0-6[a]	0-6[b]	0-12[c]
Study age at death (mo):	3	6	9	12	18+	3	6	9	12	18+	12	18	18+
No. of animals:	20	20	20	20	26	20	20	20	18	22	10	16	24
All lesions	0	0	0	0.4[d]	0.6	1.6	3.0	2.3	3.6	4.9	0.4	1.1	1.2
Hyperplasia (all)	0	0	0	0.4	0.5	1.6	2.8	2.1	3.3	4.1	0.2	0.9	0.4
Diffuse	0	0	0	0	0	0.4	0.4	0.2	0.1	0.1	0	0	0
Microfocal	0	0	0	0.1	0.1	0	0	0	0	0.1	0.1	0.4	0.1
Focal	0	0	0	0.3	0.5	1.2	2.4	1.9	3.2	4.0	0.1	0.5	0.3
Neoplasia (all)	0	0	0	0	0.1	0	0.2	0.2	0.2	0.8	0.2	0.2	0.8
Benign	0	0	0	0	0	0	0.2	0.2	0.2	0.4	0.2	0.1	0.4
Malignant	0	0	0	0	0.1	0	0	0	0	0.4	0	0.1	0.4

[a] Recovery period 7 through 12 months.
[b] Recovery period 7 through 18 months.
[c] Recovery period 13 through 18+ months.
[d] Average number = total number of lesions divided by number of animals in the group at risk. Average showing the number of lesions per animal were also calculated for the number of animals with the lesion and are reported in Appendix I.

T-11007

005126

Table 14. Location of Hyperplastic and Neoplastic Epithelial Lesions of the Small Intestine in Control Mice

Sacrifice Interval (mo)	Lesion	Location: Distance from pylorus (cm) 7	14	21	28	35
3	None					
6	None					
9	None					
12	Hyperplasia (all)	1[a]	5	1		
	Microfocal		2			
	Focal	1	3	1		
18+	Hyperplasia (all)	4	8	1	1	
	Microfocal		1			
	Focal	4	7	1	1	
	Neoplasia		1			
	Malignant		1			

[a] Number of lesions.

T-11007

005126

Table 15. Location of Hyperplastic and Neoplastic Epithelial Lesions of the Small Intestine in Mice Given Captan (6000 ppm) in Diet

Sacrifice Interval (mo)	Lesion	Location Distance from pylorus (cm)					
			7	14	21	28	35
3	Hyperplasia (all)	31[a]					
	Diffuse	7					
	Focal	24					
6	Hyperplasia (all)	55	1				
	Diffuse	8					
	Focal	47	1				
	Neoplasia	3					
	Benign	3					
9	Hyperplasia (all)	41					
	Diffuse	3					
	Focal	38					
	Neoplasia	5					
	Benign	5					
12	Hyperplasia (all)	54	5		1		
	Diffuse	3					
	Focal	51	5		1		
	Neoplasia	4					
	Benign	4					

[a] Number of lesions.

Table 15. Location of Hyperplastic and Neoplastic Epithelial Lesions of the Small Intestine in Mice Given Captan (6000 ppm) in Diet (contd.)

Sacrifice Interval (mo)	Lesion	Location Distance from pylorus (cm)					
			7	14	21	28	35
18+	Hyperplasia (all)	84[a]	5	1	1		
	Diffuse	3					
	Microfocal				1		
	Focal	81	5	1			
	Neoplasia (all)	17					
	Benign	9					
	Malignant	8					

[a] Number of lesions.

Table 16. Location of Hyperplastic and Neoplastic Epithelial Lesions of the Small Intestine in Mice Given Captan (6000 ppm) in Diet for 6 or 12 Months Followed by a Recovery Period

Treatment period (mo)	Non-treatment period (mo)	Lesion	Location: Distance from pylorus (cm) 7	14	21	28	35
0-6	7-12	Hyperplasia (all)		1[a]	1		
		Microfocal			1		
		Focal		1			
		Neoplasia	2				
		Benign	2				
0-6	7-18	Hyperplasia (all)	5	5	4	1	
		Microfocal	2	4	1		
		Focal	3	1	3	1	
		Neoplasia (all)	2		1		
		Benign	1				
		Malignant	1		1		
0-12	13-18+	Hyperplasia (all)	6	1	2		1
		Microfocal		1	1		1
		Focal	6		1		
		Neoplasia (all)	19	1			
		Benign	9				
		Malignant	10	1			

[a] Number of lesions.